Parasitic Diseases Panels

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Guidelines

Parasitic Diseases Panels

The Parasitic Diseases Panels have a primary interest in research on human helminthic and protozoan diseases, with special emphasis on vector-borne parasitic diseases, such as malaria, schistosomiasis, and filariasis, as well as emerging parasitic infections. Studies sponsored by the Panels share a long-term goal of alleviation of these diseases. Strategies include vector control, interruption of the parasite life cycle, and reduction of the amount and effects of infection by vaccination, chemoprophylaxis, or other modalities. The Panels support both basic and applied research in epidemiology, vector biology and control, parasite biology, host-parasite interactions, pathology, immunology, and biochemistry.

Five-Year Summary

Broad Goals

Parasitic diseases were designated as a particular area of interest when the U.S.-Japan Cooperative Medical Science Program was established in 1965. At the time of its inception, the Parasitic Diseases Panel was directed to focus specifically on schistosomiasis and filariasis. During the early 1980s, malaria was also identified as a rising problem and the Panels' mandate was expanded to include this disease. The Parasitic Diseases Program has continued to add other vector-borne diseases as they have become more prevalent. Protozoan and helminthic diseases continue to inflict substantial suffering on a large portion of the world's population, especially in tropical developing countries, as they have for thousands of years. The situation has worsened in many parts of the world, because of the increasing development of drug-resistant parasites and changing environmental conditions brought about by developments such as the Three Gorges Dam, in mainland China.

The U.S. and Japanese Parasitic Diseases Panels focus on the promotion and encouragement of cooperative international research on tropical infectious diseases, concentrating on multidisciplinary approaches to study parasite biology and the relationships of parasites to their vectors and mammalian hosts. In the context of the U.S.-Japan Cooperative Medical Science Program, a variety of basic and applied research studies have investigated the diverse areas of parasite biology, host-parasite interactions, pathology, immunology, biochemistry, chemotherapy, epidemiology, and vector biology. The goal of these efforts is control of major parasitic diseases in humans, through the development of vaccines, diagnostics, and improved drugs, as well as more effective control of vectors.

Progress and Accomplishments

During the past 5 years, a unique avenue has been opened in the area of functional genomics research. Better understanding of the genomes of both parasites and vectors will likely enable investigators to develop more specific vaccines, targeted disease therapies, and methods of vector control. In addition, the past 5 years have seen progress on several fronts in parasitology, especially in the development of vaccines and drugs for treatment of parasitic diseases. Scientific advances have been made according to the Panels' guidelines, in control of schistosomiasis, filariasis, malaria, and hemoprotozoan diseases.

Schistosomiasis

After mass chemotherapy to control *Schistosoma japonicum*, in Jiangxi province, China, scientists performed immunogenetic analysis of DNA in blood samples from 59 persons who were resistant or susceptible to re-infection with the parasite and in 135 local, untreated control subjects. The results indicate that the HLA-DRB1*1101 allele may impart resistance to re-infection with this parasite.

A new approach to the epidemiology of *S. japonicum* was tried in China and the Philippines by using a global information system and remote sensing as a detection technique. Satellite information on geographic conditions, such as land use and soil contents, was combined with data from epidemiologic surveillance, and analyses were performed to determine the most effective measures for control of *S. japonicum* in endemic areas. Studies have shown that the balance of phenotypes of helper T cells is an important factor in susceptibility to parasitic infections in mice. Thus, modulation of host susceptibility to parasitic infections was investigated in mice with *Schistosoma mansoni* infection, which induces responses by type 2 helper T (TH2) cells. The mice infected with *S. mansoni* rejected infection with *Strongyloides venezuelensis*, possibly because of the strong induced TH2 response. On the other hand, *S. mansoni* infection did not alter susceptibility to *Leishmania major*. Moreover, mice with schistosomiasis showed complete resistance to both *Strongyloides venezuelensis* and *Plasmodium chabaudi*, but TH2-dependent susceptibility of A/J mice to *P. chabaudi* was converted to resistance. This finding indicates that there must be unknown interactions between concurrent parasites in host animals. These studies may provide better understanding of the disease mechanisms at work in persons who live in tropical areas and have multiple parasitic infections.

In a study in Kenya, almost one-fourth of the persons infected with *Schistosoma haematobium* showed severe hepatic fibrosis. This finding suggests the presence of much greater heterogeneity in clinical symptoms of human schistosomiasis than was previously thought. More intensive studies of this phenomenon are needed, because it had been accepted that *S. haematobium* does not induce hepatic lesions.

Filariasis

Studies of lymphatic filariasis in Papua New Guinea, where transmission rates are highly variable, revealed (1) that levels of exposure to infective larvae are a probable determinant in the development of specific patterns of immunity and (2) that patients with or without microfilaremia are likely to have evidence of

chronic pathology resulting from filarial infection.

Seroepidemiologic survey is sometimes difficult to perform because of difficulty in obtaining blood samples. To overcome such problems, investigators used enzyme-linked immunosorbent assay in urine samples, for immunodiagnosis of human lymphatic filariasis. In all persons who were positive for microfilaria or circulating antigen, the assay showed positive reactivity to filarial antigen in urine. In addition, detection of immunoglobulin G4 (IgG4) in urine gave almost complete concordance with results of antibody testing in sera.

In a unique study, researchers explored the possible involvement of macrophages in the disappearance of circulating microfilariae in mice that had received intravenous injection of *Acanthocheilonema vitae* microfilariae from infected donor hosts, *Millardia meltada* mice. Together with results from in vitro experiments, the findings in this study suggest that activated macrophages are involved in the disappearance of circulating microfilariae in mice.

Malaria

Apparently encouraged by a new grant for malaria research at the molecular level, from the Japanese Ministry of Education, Science, Culture, and Sports, scientists in Japan conducted extensive research on malaria and other hemoprotozoan infections during the past 5 years. Typical examples of this research are presented here.

One study revealed a potential vaccine candidate–serine repeat antigen (SERA), a 126-kilodalton protein produced at the late trophozoite and schizont stages of *Plasmodium falciparum*. Squirrel monkeys received injection of a recombinant N-terminal domain of SERA (SE470), which was produced in *Escherichia coli* by using a synthetic gene that expresses amino acids of SERA. These injections induced specific antibodies in all monkeys and significantly reduced parasitemias. Furthermore, sera from immunized monkeys inhibited the growth of *P. falciparum* in vitro, and affinity-purified mouse antibodies against SE470 agglutinated schizonts and merozoites efficiently inhibited the growth of the parasite in vitro. A related study examined whether human sera contained antibodies against SE470 in natural infections in an area of intense malaria transmission in northern Uganda. The level of IgG3 correlated with clinical immunity in children younger than 10 years old, and affinity-purified human IgG3 specific to SE470 inhibited parasite growth.

To discover a method of blocking transmission of *Plasmodium berghei* in the mosquito vector, a single-chain, variable fragment specific to the 21-kilodalton surface protein of the *P. berghei* ookinete (Pbs21) was constructed in a baculovirus expression system. The genes encoding variable regions of the heavy and light chains of the monoclonal antibody 3.1, which is directed against Pbs21 and inhibits the development of oocysts in the mosquito midgut, were cloned and assembled as an scFv gene. A recombinant scFv gene bound to native Pbs21 on the surface of the P. berghei ookinete and blocked the development of more than 93% of the oocysts in the mosquito midgut when mosquitoes fed on mice who received the scFv gene. Thus, the recombinant scFv gene could be useful in studying the mechanism of transmission blockage.

Another study determined the complete nucleotide sequence coding for the cytochrome-c oxidase subunit III (CO III) of *Plasmodium vivax*. Sequencing of the CO III gene was completed after amplification of DNA fragments of the gene. The features of the CO III peptide of malaria parasites revealed in this study may provide information that will be useful in the search for a target for chemotherapy.

Effects of vaccination with DNA were tested in mice infected with *Plasmodium yoelii*. DNA encoding merozoite surface protein 1 (MSP-1) was injected by using a gene gun, with or without injection of DNA encoding for interleukin 12 (IL-12). Mice receiving injections of both MSP-1 and IL-12 DNA had significantly higher protection against infection with *P. yoelii.*

During 1996, the Parasitic Diseases Panels emphasized research on vaccine candidates and development of chemotherapeutic agents. Of particular importance was a study of the molecular mechanisms of resistance to chloroquine. Findings of this research could lead to development of alternative antimalarial drugs or agents to prevent or reverse resistance to chloroquine. Molecular studies of parasite antigens that may be logical drug or vaccine targets included investigation of rhoptries (apical antigens), one of which was recognized by specific antibodies in the blood of pregnant women and persons from different geographic areas, indicating its potential immunologic importance. In addition, the digestive vacuole in malarial parasites, where heme from blood is broken down, continues to be a potential target of drugs and vaccines. The mechanism that enables infected erythrocytes to adhere to the endothelial cells in blood vessels (cytoadherence) is also being investigated as a therapeutic target. Anti-ICAM-1 antibodies have led to a reversal of cytoadherence in mice infected with

P. yoelii, and cytoadherence was blocked by using monoclonal antibodies to the phalhesin (*P. falciparum adhesin*) epitope. Vector biologists focused on the molecular and genetic bases for refractoriness and susceptibility of invertebrate vectors to parasitic infection, with the aim of developing vaccines that would prevent transmission from vectors to humans.

A polymerase chain reaction test, based on amplification of part of the blood-stage antigen of MSP-1, was developed to track the numbers and types of malarial parasites infecting children younger than 10 years of age in Mali. This assay was found to be more accurate than traditional blood smears.

In 1997, genetic studies of severe anemia associated with *P. falciparum* were started in Papua New Guinea to determine the factors that cause a small proportion of people who have disease-susceptibility genes to develop severe disease. Also, a serological survey was conducted by using recombinant *P. vivax* Duffy binding protein as a capture antigen in enzyme-linked immunosorbent assay. The survey showed that absence of Duffy antigen was associated with anemia.

Also in 1997, an investigator at the National Institutes of Health (NIH) began to collaborate with an investigator at Ehime University, Japan, on a study to determine the primary structure of a novel *P. vivax* ookinete surface protein. The aim was to explore the possibility of producing a transmission-blocking vaccine to prevent the development of parasites in the *Anopheles* mosquito vector.

Hemoprotozoan Diseases

One team of U.S. investigators examined factors that confer human resistance to infection with visceral leishmaniasis in high-transmission areas of PiauR, Brazil. They found that high concentrations of mannose-binding lectin in the blood enhanced development of pathogenesis in patients infected with *Leishmania chagasi*, whereas low concentrations conferred protection from severe disease.

The protective mechanisms of IL-18 against infection with *Leishmania major* were investigated in a Japanese study in mice. Administration of a combination of IL-12 and IL-18 resulted in resistance in BALB/c mice that had been susceptible to infection with *L. major*. The cytokines induced production of interferon (, which led to an increase in the serum level of nitric oxide. Thus, IL-12 and IL-18 were shown to be critically involved in host resistance to infection with *L. major.*

Also in a Japanese study, an in vitro culture system of mammalian host cells (HeLa) infected with *Trypanosoma cruzi* was used for the screening of anti-*T. cruzi* agents. Using allopurinol as a positive control, scientists found that zidovudine (AZT) significantly reduced the growth of the parasite at concentrations as low as 1 mmol/L. The study findings suggest that AZT interferes with DNA synthesis rather than RNA synthesis in *T. cruzi* amastigotes and that AZT may target an enzyme such as trypanosomal DNA polymerase, which in *T. cruzi* is unique in its sensitivity to aphidicholine.

Meetings

During the past 5 years, joint panel meetings and conferences of the U.S.-Japan Parasitic Diseases Panels were held in parallel with meetings of the International Centers for Tropical Disease Research (ICTDR), in Bethesda, Maryland, and on special occasions, such as an international congress on tropical medicine and malaria, in Nagasaki, Japan, and an international meeting on parasitology, at Makuhari Messe. To propagate the Panels' activities, reports on the joint conferences held in 1996 and 1997 were published in Parasitology Today and Parasitology International, respectively. The Panels also cooperated to organize international conferences related to emerging and reemerging infectious diseases, with special reference to malaria and other parasitic diseases endemic in Asia and the Pacific Rim countries.

The 1996 meeting of the Parasitic Diseases Joint Panels featured a symposium on Emerging Parasitic Infections. Discussions of the increasing threat of emerging and reemerging parasitic diseases and how to cope with them addressed diseases such as echinococcosis, cryptosporidiosis, cyclosporiasis, and drug-resistant malaria in Africa and Southeast Asia.

The 1997 meeting of the Parasitic Diseases Panels was held in May, in conjunction with the 6th annual meeting of ICTDR, sponsored by the National Institute of Allergy and Infectious Diseases, at the NIH, in Bethesda, Maryland. Two members of the Japanese Panel presented talks at the ICTDR conference, and nine other members of the Japanese delegation attended the 3-day conference and took that opportunity to meet with U.S. and other international scientists. One Panel member presented an overview of the history and current state of parasitic disease research in Japan, and the other addressed allelic variation in the MSP-1 Gene of *P. falciparum*.

The one-day meeting of the U.S.-Japan Parasitic Diseases Panel followed the ICTDR meeting and featured lively, informal discussions of the presentations. Clinical studies were again the emphasis of this

meeting. A group of U.S. investigators reported that diagnosis of *Brugia malayi* filariasis has been facilitated by the use of scrotal ultrasonography. The procedure is noninvasive and enables physicians to assess subclinical lymphatic damage. The data confirm that positive antigen tests are evidence of active infection in otherwise healthy persons who live in endemic areas. Another diagnostic test for *B. malayi* is based on IgG4 detection of antibody to the recombinant antigen BmM14, which is highly immunogenic in humans. ICT Diagnostics (Australia) has used this antibody to develop and market a new diagnostic test for *Wuchereria bancrofti* antigen in blood collected by the finger-prick method. This test facilitates diagnosis of bancroftian filariasis in areas where the disease is endemic. Another group of U.S. investigators reported the successful use of an assay based on polymerase chain reaction and restriction fragment length polymorphism to detect Duffy blood group antigen, with use of DNA from blood samples collected in an area of Papua New Guinea in which *P. vivax* is endemic.

At the 3rd International Conference on Emerging and Reemerging Infections in the Pacific Basin, in Bali, in 1998, the Malaria Working Group focused on malaria transmission and disease in the Asian region. The group also discussed current problems, including the occurrence of *P. vivax* malaria as a major disease; the prevalence of multidrug-resistant malaria infections; differences in manifestations of severe malaria, such as the prominence of anemia and renal failure rather than cerebral malaria in Africa; and the importance of epidemic malaria.

The working group recommended (1) that governments of the Pacific Rim countries should work together to foster partnerships among scientists, to advance efforts in malaria research and control and (2) that working plans should include the establishment of a regional training center, sponsorship of collaborative research programs, and provision of the facilities necessary to conduct the studies proposed by the working group. Thus, as described in the Report of the Parasitic Infections Working Group, at the 4th International Conference, in Bangkok, Thailand, in 1999, a seeding grant program has been implemented to promote collaborative projects between investigators in Japan and in other Asian countries where parasitic diseases are endemic. This program is also expected to provide networking potential for cooperation among developing countries for training, research, and information exchange under the Hashimoto Initiative on Global Parasitic Diseases Control.

The 33rd annual joint meeting of the Parasitic Diseases Panels, in Makuhari, Chiba, Japan, was held in August 1998, during the 9th annual meeting of the International Congress of Parasitology (ICOPA). The conference featured a symposium on resistance to praziquantel in helminths. One U.S. scientist presented an overview of studies of praziquantel-resistant schistosomes. Another U.S. scientist reported on development of resistance to praziquantel among species of *Schistosoma mansoni* in patients in Egypt. He proposed development of an assay for the miricidial stage of the parasite that could prove to be appropriate in field studies, for detection of drug resistance in schistosomes. Also at this meeting, the chair of the U.S. Panel discussed his study of polymorphisms in a Duffy blood group promoter and the relationship of these polymorphisms to induction of protection against *P. vivax* infection in Papua New Guinea. At the ICOPA conference, a U.S. scientist presented data from her studies of the Rhop-3 rhoptry protein recovered from cerebrospinal fluid of children infected with *P. falciparum* in Zambia. Enzyme-linked immunosorbent assay of cerebrospinal fluid showed that 69% of the children were positive for anti-*Plasmodium* IgG reactivity. Another U.S. investigator reported detection of correlates of immunity against *S. mansoni* in baboons, which are natural hosts of the parasite. His results paralleled the observation by other investigators that partial resistance to reinfection was conferred by natural infection in human adolescents after repeated natural infections.

Future Goals

Members of the U.S.-Japan Cooperative Medical Science Program have emphasized the importance of research on emerging and reemerging infections, particularly those occurring in the Pacific Rim. Members of the Parasitic Diseases Panels attended conferences on emerging infections, in Bali and Bangkok, Thailand. These meetings were convened to discuss alterations in the epidemiology and pathology of numerous reemerging parasitic helminth infections, such as schistosomiasis and lymphatic filariasis. Other parasitic infections discussed included cysticercosis, leishmaniasis, hydatid disease, and drug-resistant malaria, as well as infection with food-borne trematodes, intestinal nematodes, *Toxocara*, and opportunistic protozoa, such as *Cryptosporidium, Toxoplasma,* and *Pneumocystis*. The Panels working group discussed the following topics:

1. Identification of the factors responsible for altering epidemiologic patterns of parasitic disease in Asia, such as concurrent infection with HIV, drug resistance of parasites,

environmental impact of economic development, and assessment of disease burden

2. Application of the following existing research and control resources to develop therapy for these parasitic diseases

- World Health Organization (WHO) program of chemotherapy for filariasis

- WHO program of chemotherapy for persons infected with *Schistosoma japonicum*

- Hashimoto Initiative on Global Parasitic Diseases Control, to pursue active collaborations among investigators in the United States, Japan, and countries where the parasitic diseases are endemic, and application for seed grants to leverage funds from other agencies for long-term studies of parasitic diseases

- NIH-supported programs

- Internet resources for communication

3. Identification of new ways to improve research capacity and infrastructure that will facilitate control of these parasitic diseases by the following means:

- Development and use of recombinant antigens for improved diagnostics

- Development and use of reagents and protocols for detection of drug resistance

- Vaccine technologies and novel vaccine targets and structures

- Discovery and development of genetic markers for susceptibility and resistance to specific diseases in targeted populations

- Creation of surrogate markers for early detection of infection and for epidemiologic studies

The Hashimoto Initiative, presented at the 1997 Denver Summit meeting between Japanese Prime Minister Hashimoto and U.S. President Clinton, proposed encouragement of collaborations among scientists from Japan, the United States, and countries where the parasitic diseases are endemic. This initiative stressed the need for international cooperation and increased diligence in developing new methods to control parasites. Subsequent to presentation of the Hashimoto Initiative, the Japanese government started a working group on global parasite control. Teams from this working group were dispatched to developed and developing countries and to the WHO headquarters. An international conference on parasite control, sponsored by WHO, was held in Tokyo, Japan, in December 1997. The participants at the conference proposed the following measures for effective control of parasites:

- International cooperation for the efficient implementation of parasite control

- Active pursuit of research that provides a scientific basis for parasite control

- Implementation of effective projects to control parasites

- Strengthening of the capabilities of the G8 countries to control parasitic diseases

The Parasitic Diseases Panels discussed implementation of these proposals, at their joint meeting, in Nagoya, Japan, on July 26, 2000.

The Panels also discussed opportunities to work with the World Bank in defining a multilateral approach to malaria research and training in the Solomon Islands. The World Bank will finance by credit the Solomon Islands Health Sector Development Project. According to Mead Over, of the World Bank, the government of the Solomon Islands will seek proposals from international collaborators interested in working (1) with the National Malaria Control Programs on operational research projects that would directly benefit those programs and (2) with WHO(s Roll Back Malaria initiative. These joint efforts would involve specific research projects and training at the masters degree level for qualified researchers in the Solomon Islands. It is anticipated that these projects will lead to longer-term relationships built on the interests of international collaborators, using resources available in the Solomon Islands, and that they will contribute to malaria control in that part of the world.

Additional discussions by the Panels centered around the activities to monitor the Multilateral Initiative on Malaria (MIM), of NIH's John E. Fogarty International Center for Advanced Study in the Health Sciences (FIC). One important area of MIM lies in stimulation and support of research on *P. vivax* malaria, particularly in Central Asia, Indonesia, Java, and Korea. *P. vivax* is more widespread globally than *P. falciparum* and its impact is likely to be even greater in the future, partly due to the parasite's developing resistance to chloroquine and primaquine. FIC expects to convene a meeting of international researchers on *P. vivax*, to solicit recommendations for research and training priorities. Through MIM, FIC also plans to collaborate with a recently formed network of Asian researchers and to attract other international investigators who want to collabo-

rate in research to meet the unique challenges presented by *P. vivax*.

Additional Objectives

- More intensive promotion of cooperative activities between U.S. and Japanese scientists in basic and operational research in parasitology

- Establishment of potential for networking between developed and developing countries and among developing countries to cooperate in training, research, and information exchange, including activities such as training and technical assistance required for parasite control and cooperative research under the Hashimoto Initiative on Global Parasitic Diseases Control

- Introduction of new techniques and strategies for parasite control, including (a) use of a global information system and remote sensing as powerful tools in epidemiologic surveys, and (b) collection of data from research fields in Asia for use in designing effective measures against the future spread of parasitic disease

- Advancement of research activities in molecular biology, molecular parasitology, and genome analyses in several important human parasites and in humans, which together are expected to enable substantial progress in diagnosis, vaccine development, biology of parasitism, and immunopathogenesis

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